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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,522	05/02/2002	Marc G. Jacquemin	522-1769	5981

7590 12/15/2004

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,522	JACQUEMIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004 and 29 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 9/20/04 and 10/29/04, is acknowledged.

2. Claims 49-57 are pending and under examination as they read on a monoclonal antibody against factor VIII, a cell line, fragments, and a composition thereof.

3. The claim to priority to PCT/EP00/06677, and 60/143,891 filed 07/14/1999, disclosed in the Oath/Declaration, needs to be included as the first sentence of the specification following the title.

4. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figures 6-9, on page 11, lined 20-30 have describe four VH and VL sequences of BO2C11 and KRIX 1 that each must have a sequence identifier. Correction is required.

5. Claims 50 and 53 are objected to because of the following informalities: the alternative operator "or", which should be only before the last term of a series, has been recited twice, once after Fab` and the second time after $F(ab`)_2$. Correction is required.

6. In view of the amendment filed on 10/29/04, the following rejections are necessitated by the amendment.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 57 is indefinite for being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the return of the B-lymphocytes to the blood of the human because the preamble recites obtaining a monoclonal antibody form the blood of a human.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 50, 52-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

(a) The phrase "scFv" claimed in claim 50, line 1, and 53 line 6, line, 6, (b) the phrase "having the capacity to partially inhibit fVIII activity" claimed in claims, 50, line 3, claim 53, line 7 1-2, claims 56-57, last line, (c) the phrase "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" claimed in claim 52, line 2-4 and (d) the phrase "having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in a physiological excess" claimed in claim 52, lines 5-6 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 9/25/04 does not point to the specification for support for the newly added limitations "scFv" as claimed in claims 50 and 53, "having the capacity to partially inhibit fVIII activity" as claimed in claims 53 and 56-57 and "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" as claimed in claim 52 and "having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in a physiological excess" as claimed in claim 52. Applicant appears to draw the Examiner's attention to page 12, lines 18-20 for support of at least 80%, however, the Examiner notes that the specific paragraph of the specification refers to ligands rather than antibodies. However, the specification does not provide a clear support for such limitations, Further, Applicant appears to refer the examiner to page 16, lines 6-12, however, the at least 80% homology is referred to the intact antibody or the CDRs, rather than V_H or V_L sequences. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

11. In view of the amendment filed on 10/29/04, only the following rejections are remained.

12. Claim 49-51 and 53-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 5/20/04.

Applicant's arguments, filed 9/20/04, have been fully considered, but have not been found convincing.

Applicant argues that the deposit is present in a public depository and in accordance with rule 9.1 or the Budapest Treaty. Further, Applicant presents a copy of the receipt provided to Applicant by the BCCM indicating the deposit was received under the Budapest Treaty, as well as the requested statement with regard to its availability. Applicant contends that given the statement and Applicant's declaration Applicant maintains that the requirements of section 112.

While the Examiner acknowledges the copy receipt provided by BCCM indicating the deposit of KRIX-1 cell line, however, no a statement was not find in the application regarding the availability or the deposited antibody. Regarding the unsigned Declaration, no reference to the availability of the deposited KRIX-1 antibody.

13. Claims 52-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically binds C1 domain of factor VIII, does not reasonably provide enablement for a purified monoclonal antibody or fragment thereof comprising a variable heavy sequence being at least 80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9, said monoclonal antibody having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in a physiological excess in claim 52 or a pharmaceutical composition for the prevention or treatment of disorders of hemostasis and resulting pathologic conditions in mammals, comprising as an active ingredient the monoclonal antibody produced by the cell line named KRIX 1 deposited with the Belgian Coordinated Collections of Micro-organisms, under accession number LMBP 5089CBm or an antigen-binding fragment Fab, Fab` or F(ab`)2 or scFV thereof, said fragment binding the C1 domain of fVIII and having the capacity to partially inhibit fVIII activity in admixture with a pharmaceutically acceptable carrier in claim 53, a method of obtaining a monoclonal antibody from a non-human mammal comprising the steps of selecting a non-human mammal having a modification being with respect to a wild type FVIII protein and lying in the C1 domain of the FVIII protein in claim 56, or a method of obtaining a monoclonal antibody from the blood of a human having a modified and partially functional FVIII protein, the modification being with respect to wild type protein and lying in the C1 domain of the protein in claim 57. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. Claims 52-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody which specifically binds C1 domain of factor VIII.

Applicant is not in possession of a purified monoclonal antibody or fragment thereof comprising a variable heavy sequence being at least 80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9, said monoclonal antibody having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in a physiological excess in claim 52 or a pharmaceutical composition for the prevention or treatment of disorders of hemostasis and resulting pathologic conditions in mammals, comprising as an active ingredient the monoclonal antibody produced by the cell line named KRIX 1 deposited with the Belgian Coordinated Collections of Micro-organisms, under accession number LMBP 5089CBm or an

antigen-binding fragment Fab, Fab` or F(ab`)2 or scFV thereof, said fragment binding the C1 domain of fVIII and having the capacity to partially inhibit fVIII activity in admixture with a pharmaceutically acceptable carrier in claim 53, _a method of obtaining a monoclonal antibody from a non-human mammal comprising the steps of selecting a non-human mammal having a modification being with respect to a wild type FVIII protein and lying in the C1 domain of the FVIII protein in claim 56, or a method of obtaining a monoclonal antibody from the blood of a human having a modified and partially functional FVIII protein, the modification being with respect to wild type protein and lying in the C1 domain of the protein in claim 57.

There is no described or art-recognized correlation or relationship between the structure of the invention, the modified C1 domain of the FVIII and it's partially function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants C1 domain of FVIII which retain the features essential to the instant invention. Similarly, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of monoclonal antibodies comprising a variable heavy sequence being at least 80 % identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9 which retain the partially inactivating factor VIII activity.

Applicant's arguments, filed 9/20/04, have been fully considered, but have not been found convincing.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibody as defined by the claims which may contain less than the full complement of CDRs (due to up to 20% modifications of VH and/or VL) from the heavy and light chain variable regions of an fVIII antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required

to produce the antibodies of invention commensurate with the scope of the claims from the written disclosure alone.

Further, the antibody fragments of claim 52 are not limited to antibody fragments that have the capacity of partially inactivating factor VIII activity when present in a physiological excess. Therefore, the antibody fragments of claim 52 are any antibody fragments that have at least 80% to amino acid sequences of VH and/or VL of the antibody KRIX 1, irrespective of their binding activities.

Further, claims 56-57 recite modification in the C1 domain of the FVIII, however the specification does not teach what modification in the C1 domain would lead to partial function of FVIII protein. The specification fails to provide sufficient guidance regarding the changes and modifications that can be made to the C1 domain of the FVIII protein while retaining function. The specification fails to provide sufficient guidance as to which amino acid of C1 domain of the FVIII protein is essential for maintain its biological activity and which changes can be made in the structure of C1 domain of the FVIII protein and still maintained the same function. Table 1 of the specification provides modification in FVIII domains (not only C1 domain), wherein KRIX 1 inhibited the activity of all mutated factor VIII molecules tested except those carrying the mutation Arg2150His. Therefore, it is unclear which mutation in the C1 domain of FVIII would lead to the partially function of the antibody.

Applicant submits that the specification provides a full characterization of KRIX-1 antibody including the sequence of its variable domains. Further, the specification provides a test method for assaying FVIII inhibitory activity. Applicant argues that the skilled person could, with a limited effort and based on standard methods in the art, produce minor variants of this antibody having a similar usefulness. Applicant provides an example using the information in the specification on epitope-mapping and assaying FVIII activity, a large set of antibodies derived from KRIX-1 by random mutations in the variable chains can be screened in parallel for binding to the C1 domain. Applicant contends that antibodies can than further be screened for there inhibiting properties.

However, while claim 52, recites at least 80% identical to the amino acid sequence of VH or VL of KRIX-1 antibody, no need for the skilled artisan to map and know the epitope, since the VH and VL are known. However, Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of antibodies/antibody fragments thereof with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of figures 8 or 9 would have been altered such that the resultant antibody would have retained the function of partially inactivating factor VIII activity when present in a physiological excess. In addition, variation up to 20% of amino acid sequence depicted in figure 8 (31^{20} variations) and/or figure 9 (28^{20} variations) provide a range of activities, not all which are necessarily predictive of having the capacity of partially inactivating factor VIII when

present in a physiological excess. Therefore, absent the ability to predict which of these antibodies would function as claimed for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

The claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of structurally related KRIX-1 amino acid molecule is disclosed. The artisan would not know the identity of a reasonable number of representative KRIX-1 falling within the scope of the instant claim and consequently would not have known how to make them. *Again, in order to satisfy 112, first paragraph, the specification has to teach how to make and use the polypeptides of the invention not how to identify the invention.*

Further at issue the claimed pharmaceutical composition for the prevention or treatment of any disorder of hemostasis and resulting pathologic conditions in mammals.

Applicant submits that the specification as illustrated by Example 7 discloses the use of "a physiological excess" of KRIX-1 a partial reduction of fVIII activity is obtained.

However, the claimed pharmaceutical composition is not limited to the partial reduction of fVIII activity, but recites the use for prevention or treatment of any disorder of hemostasis and resulting pathologic condition in mammals. However, an effective protocol for the prevention and treatment of disorders of hemostasis and resulting pathologic conditions in mammals is subject to a number of factors which enter the picture beyond simply the administration of the therapeutic composition in an acceptable formulation. Demonstrating partial inhibition of fVIII by KRIX-1 antibody cannot alone support the predictability preventing and treating any disorder of hemostasis and resulting pathologic conditions through administration of the appropriate formulation. The specification does not provide sufficient teaching as to how it can be assessed that prevention was achieved after the administration of the therapeutic composition of the invention. Further, the specification does not provide sufficient teachings as what is the target population that needs the prevention treatment.

14. The declaration, in unsigned form, filed under 37 CFR1.132 by Dr. Maro Jacquemin on 9/20/04 is defective because: it is not signed inventor Dr. Maro Jacquemin and Dr.Jean-Marie R. Saint-Remy.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 56-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacquemin et al (Blood. 1998 Jul 15;92(2):496-506) (IDS Ref).

Jacquemin *et al* a method of obtaining monoclonal antibodies from a hemophilia A patient (BO) (having a modified and partially functional fVIII protein) with inhibitor to fVIII Jacquemin et al teach that the hemophilia A patients received fVIII infusions (wild-type) (see Abstract and page 503, under Discussion in particular). Peripheral blood mononuclear cells were prepared by Ficoll-Hypaque density centrifugation using standard methods (see page 497, under Peripheral Blood Lymphocytes and cell lines in particular). Jacquemin et al further teach that PBMCs were immortalized using Epstein-Barr virus (EBV) supernatant (B95-8 strain). Culture supernatants were tested in enzyme-linked immunosorbent assay (ELISA) for the presence of anti-fVIII antibodies. Positive cell lines were cloned (see page 497, under Immortalization of Human PBMCs and page 499 under Results in particular).

While the prior art teachings may be silent as to "the modification being with respect to a wild type FVIII protein and lying in the C1 domain of the FVIII protein" per se; the method, the patient used in the reference method are the same as the claimed method. Therefore "the modification being with respect to a wild type FVIII protein and lying in the C1 domain of the FVIII protein" is considered inherent properties

The reference teachings anticipate the claimed invention.

17. In view of the amendment filed on 10/29/04, the following rejections are necessitated by Applicant disclosure in the remarks under 102 rejection, that LE2E9 is Krix-1 antibody.

18. Claims 49-53, 55 and 57 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacquemin et al (Blood. VO. 92, 10 suppl. 1 Part 1-2, pp710., 11/15/1998), (of record).

Jacquemin et al teach a monoclonal antibody produced by the cell line name LE2E9 (Krix-1) and its fab fragment that inhibits the binding of wild type FVIII C1 domain. Jacquemin et al further teach that an IgG4 human monoclonal antibody, LE2E9 was obtained by in vitro immortalisation of memory B lymphocytes of a mild hemophila A patient (LE) who developed an immune response towards wild type FVIII but remained tolerant toward self FVIII carrying the mutation Arg2150His. Gilles et al teach the use of antibody in different assays which requires the antibodies to be in solutions.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 9/20/04, have been fully considered, but have not been found convincing.

Applicant argues that the cited article features both inventors and was published on July 15, 1998, which is less than one year before the filing of the priority application of the present application.

However, the cited reference is still considered by others since it has 10 additional authors, in addition to the two inventors.

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

20. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquemin (Gilles) et al (off record) or Jacquemin et al (Blood. 1998 Jul 15;92(2):496-506) (IDS Ref) each in view of U.S. Patent No. 6,602,015.

The teachings of Jacquemin (Gilles) et al references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a non-human mammal.

The `015 patent teaches the autoantibodies are polyclonal antibodies and that monoclonal antibodies are prepared by isolating lymphocytes from the so-identified animals, producing a plurality of hybridomas from the lymphocytes and screening the monoclaonal antibodies produced by the hybridomas to identify monoclaonal antibodies (col. 2, lines 61-66 in particular). The `015 patent teaches that peripheral blood lymphocytes of an animal identified as having rate enhancing autoantibodies for a particular substrate can be stimulated to grow in culture and, therefore, can be immortalized using methodologies well known in the art. For example, the lymphocytes can be so stimulated using a virus, a chemical agent or a nucleic acid (e.g., an oncogene). A particularly advantageous virus for immortalization is Epstein Barr virus (EBV). Thus, rate enhancing autoantibodies can be produced by the transformed cells. The so transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies having rate enhancing activity for a given substrate the transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies (col., 8, lines 34-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the monoclonal taught by Jacquemin et al using the method taught by the `015 patent by isolating lymphocytes from the so-identified animal.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such a method would provide a reliable source of large amounts of monoclonal antibodies as taught by `015 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 50 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable Jacquemin (Gilles) et al in view of Owens *et al* (1994).

The teachings of Jacquemin et al have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment in claims 50 and 53.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Jacquemin et al as a as a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment as taught by Owens et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore,

the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 9/20/04, have been fully considered, but have not been found convincing.

Applicant argues that the cited article features both inventors and was published on July 15, 1998, which is less than one year before the filing of the priority application of the present application.

However, the cited reference is still considered by others since it has 10 additional authors, in addition to the two inventors.

22. Claim 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquemin (Gilles) et al in view of U.S. Patent No. 6,127,337.

The teachings of Jacquemin (Gilles) et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the pharmaceutical composition further comprising a therapeutically effective amount of a thrombolytic agent.

The `337 patent teaches in the combinations, the thrombin inhibitor and the thrombolytic agent work in a complementary fashion to dissolve blood clots, resulting in decreased reperfusion times and increased reocclusion times in patients treated with them. Specifically, the thrombolytic agent dissolves the clot, while the thrombin inhibitor prevents newly exposed, clot-entrapped or clot-bound thrombin from regenerating the clot. The use of the thrombin inhibitor in the formulations of this invention advantageously allows the administration of a thrombolytic reagent in dosages previously considered too low to result in thrombolytic effects if given alone. This avoids some of the undesirable side effects associated with the use of thrombolytic agents, such as bleeding complications. (col., 8, lines 34-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combined the pharaceutical composition taught by Jacquemin et al with a thrombolytic agent taught by the `337 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because thrombolytic agent work in a complementary fashion to dissolve blood clots, resulting in decreased reperfusion times and increased reocclusion times in patients treated with them as taught by `337 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
December 10, 2004

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